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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,351	06/07/2002	Stace Lindsay	06727/008002	8638
21559	7590	01/30/2007		
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			EXAMINER BERTOGLIO, VALARIE E	
			ART UNIT	PAPER NUMBER
			1632	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/30/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/030,351	LINDSAY ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,6-9 and 12-24 is/are pending in the application.
- 4a) Of the above claim(s) 2,4,8,9 and 12-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6,7 and 21-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/24/2006</u> | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's reply dated 11/24/2006 has been entered. Claims 3,5,10-11 are cancelled. Claims 21-24 have been added. Claims 2,4,8,9,12-20 are withdrawn. Claims 1,2,4,6-9,12-24 are pending and claims 1,6,7 and 21-24 are under consideration in the instant office action.

#### ***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The rejection of claims 10 and 11 under 35 U.S.C. 112, first paragraph, enablement is withdrawn in light of Applicant's cancellation of the claims.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,6 and 7 remain rejected and newly added claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deboer (1997, US 5,633,076; IDS) or Clark (1994, US 5,322,775;IDS) or Lubon (1998, US 5,831,141; IDS) in view of Morinaga (1983, PNAS, Vol. 80, pages 4604-4608; IDS) and Bennett (1997, Breast Cancer Research and Treatment, Vol. 45, pages 169-179; IDS) for reasons of record set forth at pages 10-13 of the previous office action dated 03/22/2005.

It is noted that newly added claim 21 appears to be identical to previously pending claim 3, now cancelled, which was originally included in this rejection. Claim 22 appears to be identical to previously pending claim 5, now cancelled, which was originally included in this rejection.

Newly added claim 23 is drawn to a method of using the recombinant mammal that produces and secretes rHuAFP into its milk of claim 21 to prepare rHuAFP, which is made obvious by each of DeBoer, Clark and Lubon as set forth at pages 11-12 of the office action dated 03/22/2005, given the obviousness of the rHuAFP-producing mammal as included in the original rejection (see pages 10-13 of the previous office action dated 03/22/2005). Claim 24 is drawn to adding a method step to the method of preparing rHuAFP by purifying it, which is also made obvious by the above-cited teachings.

Each of DeBoer, Clark and Lubon taught making transgenic mammals that produce and secrete a recombinant protein of interest into the milk of said mammal. As set forth in the rejection of record, the vast array of mammals used and proteins produced by said mammals renders obvious the method of making a mammal to express any protein of interest and to collect it in the milk given that Morinaga provided the additional teachings and motivation to apply the methods of each of DeBoer, Clark and Lubon to produce rHuAFP in the milk of mammals. Each of DeBoer, Clark and Lubon taught collecting and purifying their respective recombinant proteins, rendering it obvious to do so to rHuAFP as well, as required by newly added claims 23 and 24.

Applicant's arguments pertaining to this rejection have been fully considered and are not found persuasive.

Applicant argues that the method of Bennett, which relates to the production of rHuAFP using *E. coli*, was not met with any dissatisfaction and was quite successful (page 9, paragraph 2 of Applicant's Remarks). Applicant argues that the lack of glycosylation of rHuAFP using a prokaryotic system does not

Art Unit: 1632

render the protein nonfunctional, indicating that use of a mammalian system would not be preferred over the prokaryotic system of Bennett.

In response, that Bennett provides a means of producing rHuAFP in large quantities differing from that of the instant invention does not overcome the instant rejection. Bennett supports a motivation to make recombinant AFP and is not relied upon as a primary reference to seek an alternative method or to use a mammalian system in AFP production. Bennett merely exemplifies the interest in producing large quantities of AFP. It is obvious to use the claimed mammalian system to make any protein of interest as demonstrated by each of DeBoer, Clark and Lubon. Bennett teaches that AFP is a protein of interest.

Applicant argues that the lack of glycosylation of rHuAFP using an *E.coli* system is preferred as it removes the difficulties in determining the activity of the protein (page 9, paragraph 3 of Applicant's Remarks).

In response, this argument appears to be taken out of context. Bennett suggests that there was a possibility that molecules that may be bound to AFP or copurify with it could affect the activity of purified AFP. By purifying the rHuAFP from a prokaryotic system, it is less likely that activity of the purified rHuAFP is due to these other factors. This is an isolated advantage in determining more precisely AFP activity and has no impact on the obviousness and/or motivation to carry out the instant invention in a mammalian system.

Applicant poses the argument that Bennett expressed no dissatisfaction with having to purify the rHuAFP from inclusion bodies formed using the prokaryotic system and therefore, does not indicate an advantage of the mammalian system where such solubilization and refolding steps are not necessary.

Art Unit: 1632

In response, regardless of any dissatisfaction Bennett may or may not have felt about the additional steps required in obtaining rHuAFP using *E. coli*, the mammalian system has the advantage of not requiring those steps. Bennett merely provides the evidence demonstrating that these additional steps were necessary and that they are steps that do not need to be carried out in the mammalian system. Importantly, Clark taught that solubilization and refolding prior to purification is a process that is not practical for large-scale preparation (for example, see Clark, col. 1, lines 23-27). Whether or not the solubilization and refolding was a large burden to the scientist does not overcome the beneficial nature of not having to carry out those steps. However, it is also noted, that the post-filing art demonstrates the production of rHuAFP in the milk of transgenic goats, and notes, as well, that although *E. coli* expression systems have been used to produce AFP, the refolding of the protein from inclusion bodies is not practical for commercial production (Parker *et al.*, **Protein Expression and Purification**, 38:177-183, 2004, specifically, page 178, paragraph 1). Notably, Parker *et al.* state that the large-scale production of proteins in milk is cost-effective and offers benefits over use of yeast and mammalian cell culture systems, in addition to the benefits of avoiding protein refolding experienced in *E. coli* (page 178, paragraph 2).

Applicant argues that the first successful transgenic mouse occurred over 25 years ago and a patent was issued in 1988. Production of recombinant proteins was demonstrated in mice in 1987, in rabbits in 1990, in swine, sheep and goats in 1991. Despite this, not one reference taught expression and secretion of rHuAFP in the milk of a transgenic mammal. Applicant notes nearly 400 scientific publications since 1999 describing expression and secretion of a variety of recombinant human proteins, with none teaching expression of rHuAFP in its milk (page 10, paragraph 3-page 12, paragraph 1). Because the prior art does not demonstrate any inquiry into the production of a transgenic mammal capable of secreting rHuAFP into its milk, the claimed invention is not obvious. Applicant continues

Art Unit: 1632

along the same line of argument in stating that the genus of proteins made using the mammalian system of the instant invention does not render obvious the claimed species (page 12, paragraph 2-page 14, paragraph 1).

In response, Applicant's argument that the claimed invention is not obvious because it is not present in the prior art is not persuasive. The lack of teachings in the art as set forth by Applicant is relevant in terms of anticipation. The lack of one carrying out fully the claimed invention fails to render it nonobvious. In a review of the MPEP, no reference could be found for non-obviousness to be based on the absence of, presumably in view of applicant's argument, anticipatory references. The standards for obviousness are teachings, motivation and suggestion set forth in the cited references. The combined references of Deboer, Clark, Lubon, Morinaga and Bennett clearly provide the requisite standards, as set forth in the rejection mailed 03/22/2005. There is no standard regarding the age of a technology as related to the invention. The age difference between a reference and an invention does not affect the use of the reference to formulate an obviousness rejection. See MPEP 2145.

Ex parte Robert A. Meyer, 6 U.S.P.Q.2D (BNA) 1966 January 13, 1988 states:

Appellant has argued that the long period of time which elapsed between the issuance of the Gandrud and Hunt patents is evidence of unobviousness and has cited decisions in support of this position. However, the mere age of a reference is not persuasive of unobviousness [\*6] absent evidence that the art tried and failed to solve the problem notwithstanding knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977); *In re McGuire*, 416 F.2d 1322 163 USPQ 417 (CCPA 1969).

Should applicant have any authority through which to base their arguments that the lack of anticipatory references is evidence of non-obviousness, they are invited to submit such. Applicant has not demonstrated any unexpected results and not demonstrated on the record that the instant invention is not obvious in light of the combination of teachings of the prior art of record.

Applicant argues that the Examiner need find motivation or suggestion to make the claimed invention in light of the prior art teachings and that the art fails to provide any motivation or suggestion to produce Applicant's transgenic mammal (page 13, paragraph 2).

In response, art teaching both the mammalian system and its use in making rHuAFP would be anticipatory art. The combination of references set forth in the rejection of record, along with the summary of the art that Applicant has presented in their arguments, while not of record in the instant rejection, clearly supports use of the claimed mammalian system for producing any recombinant protein. The art of record, namely Morinaga and Bennett, clearly set forth the remaining necessary teachings and motivation to render the instant invention obvious.

Applicant argues that the rejection is established by impermissible use of hindsight reasoning (pages 14-16 of Applicant's reply).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

It is noted that Applicant points to "Examiner's primary reference, Bennett" (page 14, last paragraph). It is very important to note that Bennett is not the primary reference relied upon for the instant rejection. In fact the primary references, DeBoer, Clark and Lubon render obvious the use of the claimed mammalian system to make any recombinant protein with a reasonable expectation of success. Bennett provides evidence of the motivation and desire to produce rHuAFP. The success of Bennett's prokaryotic



Art Unit: 1632

system is not relevant to applying the mammalian system, well known in the art, to rHuAFP. In general it appears Applicant's arguments are relevant to a rejection under anticipation rather than obviousness.

Art Unit: 1632

*Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Valarie Bertoglio

Examiner

Art Unit 1632